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# Update on the State of the Science: Sleep-Wake Disturbances in Adult Patients With Cancer

Ann M. Berger, PhD, RN, AOCN<sup>®</sup>, FAAN

**P**atients with cancer and their caregivers often experience sleep-wake disturbances, particularly insomnia. However, this pervasive and distressing symptom is widely ignored. These disturbances were illuminated at a State of the Science Conference on Sleep-Wake Disturbances in People With Cancer and Their Caregivers in Pittsburgh, PA, in July 2004. The conference was funded primarily by the National Cancer Institute (R13 CA108758-01), the Oncology Nursing Society (ONS), and the ONS Foundation. An interdisciplinary group of nurse scientists, a physiologist, a psychiatrist, and a psychologist synthesized the current knowledge and discussed key issues. The discussions regarding the current scope of the issue, terminology, mechanisms, measurement, interventions, and nursing implications for practice, education, and research identified by the conference participants were summarized and disseminated in Berger et al. (2005).

This article updates the state of the science in sleep-wake disturbances, focusing on insomnia in adult patients with cancer. The author acknowledges the limitation of focusing only on insomnia in adult patients. Also needed are complementary reviews of insomnia in children, adolescents and young adults with cancer, and caregivers of patients with cancer as well as other sleep disorders in adult patients with cancer. In the time since the conference, sleep-wake disturbances have received increased focus and the trend influenced the decision to limit the focus of this article to insomnia in adult patients with cancer. Included are sections on prevalence, mechanisms, measurement, interventions, and implications for practice, health policy, education, and research. The author's goal is to inspire excellence in nursing related to reducing negative health outcomes from sleep-wake disturbances.

Sleep-wake disturbance is a general term used to describe the symptom of perceived or actual alterations in night sleep with resultant daytime impairment (Berger

**Purpose/Objectives:** To update the state of the science on sleep-wake disturbances in adult patients with cancer, focusing on insomnia in the areas of prevalence, mechanisms and models, measurement, interventions, and implications for practice, health policy, education, and research.

**Data Sources:** Published articles, books, book chapters, MEDLINE<sup>®</sup>, CINAHL<sup>®</sup>, and PsycINFO computerized databases.

**Data Synthesis:** Since the 2004 conference on Sleep-Wake Disturbances in People With Cancer and Their Caregivers, an increased focus has existed on the prevalence and distress experienced by patients with cancer with sleep-wake disturbances, particularly insomnia. Evidence suggests that altered physiology directly related to the cancer process may play a prominent role in disrupting sleep, circadian rhythms, and hypothalamic-pituitary-adrenal axis-regulated processes. Reliable and valid objective and subjective measurements for screening and assessing sleep-wake disturbances are ready for use in clinical and research settings, and an increasing amount of intervention studies have reported sleep-wake outcomes in adult patients with cancer.

**Conclusions:** Cognitive behavioral therapy interventions are likely to be effective, but effectiveness has not been established for complementary, education or information, or exercise interventions.

**Implications for Nursing:** Multidisciplinary research teams should test the effectiveness of interventions to reduce sleep-wake disturbances in adult patients with cancer. Settings should create the infrastructure to initiate and sustain evidence-based oncology nursing practice, clinicians should educate the public about sleep, and public policies should promote adoption of healthy sleep patterns and early diagnosis and treatment of sleep disorders.

et al., 2005). The most common complaints involve difficulty in one or more of the following areas: falling asleep, staying asleep, early morning awakenings with inability to resume sleep, nonrefreshing or nonrestorative sleep, and daytime sleepiness. This term refers to the symptom when a specific diagnosis of a sleep disorder has not been made (Savard & Morin, 2001).

Communication related to sleep-wake disturbances in adult patients with cancer should use terminology consistent with that employed by the American Academy of Sleep Medicine ([AASM], 2005). The major types of currently recognized sleep and arousal disorders include insomnia, sleep-related breathing disorders, hypersomnias, circadian rhythm sleep disorders, parasomnias, and sleep-related movement disorders.

Insomnia is the most common sleep-wake disturbance in healthy adults and in patients who have cancer (Sateia & Lang, 2008) and is the focus of this article. General criteria for insomnia are presented in Figure 1. The subtypes most applicable to new-onset insomnia in patients with cancer are adjustment insomnia (acute insomnia) and insomnia from a medical condition (comorbid insomnia). Daytime sleepiness represents disturbed alertness or wakefulness and should be included when determining the prevalence of insomnia and other sleep disorders. Timing of insomnia is referred to as acute, transient (less than one month), or chronic (one month or longer).

Insomnia is a significant issue because evidence has confirmed that insomnia in adults is associated with other symptoms, including fatigue (Berger & Mitchell, 2008; Wielgus, Berger, & Hertzog, 2009) and decreased quality of life (QOL) a few days prior to cancer treatment (Ancoli-Israel et al., 2006; Berger, Farr, Kuhn, Fischer, & Agrawal, 2007) and following treatment (Byar, Berger, Bakken, & Cetak, 2006; O'Donnell, 2004). In the first year after a cancer diagnosis in older adults, the co-occurrence of pain, fatigue, and insomnia has been associated with increased risks of death, loss to follow-up, and increased reports of other symptoms (Kozachik & Bandeen-Roche, 2008).

The example of breast cancer illustrates the impact of sleep-wake issues in patients with cancer. Insomnia and fatigue are among the most prevalent and distressing symptoms among breast cancer survivors (Baker, Denniston, Smith, & West, 2005; Bower, 2008; Cappiello, Cunningham, Knopf, & Erdos, 2007; Carpenter et al., 2004). Persistent fatigue and psychological distress, both common consequences of poor sleep, have been shown to predict several important breast cancer outcomes, including the duration of fatigue (Bower et al., 2006), QOL (Fiorentino & Ancoli-Israel, 2007), recurrence-free periods, and overall survival (Groenvold et al., 2007).

Increasing numbers of breast cancer survivors during the past 10 years (American Cancer Society, 2008) have raised awareness of the urgent need to improve the treatment of the most common cancer-related symptoms, including insomnia, to improve QOL (Bower, 2008). Reports using cluster analysis have identified distinct patient subgroups that experience higher levels of several symptoms, including insomnia, and report the lowest QOL compared to other groups (Barsevick, 2007; Miaskowski et al., 2006; Pud et al., 2008). These

findings have led to efforts to increase understanding of the roles that phenotypic characteristics (physiologic or environmental) and genetics play in the symptom experience in addition to demographic, disease, and treatment characteristics.

## Prevalence

Since the 2004 conference, no new study has reported the prevalence of sleep-wake disturbances in a large and diverse sample of adults with various types and stages of cancer. A population-based sample of women in the United States who had completed primary treatment for early-stage breast cancer participated in a survey designed to identify the presence and frequency of symptoms. A single item measuring sleep disturbances on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire was reported as "disturbed" by 57% of 1,372 survey respondents after initial surgical treatment ( $\bar{X} = 7.2$  months) (Janz et al., 2007). Previous estimates of sleep issues in patients with cancer were 33%–40%, about twice the rate of 15%–20% in the general population (Davidson, MacLean, Brundage, & Schulze, 2002; Savard & Morin, 2001; Savard, Simard, Blanchet, Ivers, & Morin, 2001).

The incidence of sleep disturbances is increasing in the general population and in adult patients with cancer. The National Sleep Foundation (2008) reported that about 1 in 10 respondents from the general population were classified as being at risk for insomnia. On workdays, 52% of respondents reported getting the recommended seven or more hours of sleep, but 44% reported getting less than seven hours of sleep (4% missing data). The poll also indicated that 72% of the respondents surveyed were either overweight (36%) or

- Complaint of difficulty initiating sleep, difficulty maintaining sleep, or waking up too early or sleep that is chronically non-restorative or poor in quality
- Sleep difficulty occurring despite adequate opportunities and circumstances for sleep
- At least one of the following forms of daytime impairment related to the nighttime sleep difficulty is reported by the patient.
  - Fatigue or malaise
  - Attention, concentration, or memory impairment
  - Social or vocational dysfunction
  - Mood disturbance or irritability
  - Daytime sleepiness
  - Motivation, energy, or initiative reduction
  - Proneness for errors or accidents at work or while driving
  - Tension, headache, or gastrointestinal symptoms in response to sleep loss
  - Concerns or worries about sleep

### Figure 1. General Criteria for Insomnia in Adults

Note. Based on information from American Academy of Sleep Medicine, 2005.

obese (34%). In contrast, 27% were average weight and 1% were underweight. Reports have linked increased body fat and altered metabolism with disrupted sleep patterns (Bray & Young, 2007) and sleep loss with risk for obesity and diabetes (Knutson & Van Cauter, 2008). The cause and effect relationships for these associations are being investigated. Reports also link obesity as a risk factor for developing many types of cancer (Pischoon, Nothlings, & Boeing, 2008). Newly diagnosed patients with cancer who are overweight or obese and sleep deprived are more likely to have a history of or be currently experiencing sleep-wake disturbances.

## Mechanisms and Conceptual Models

Multiple factors act singly or in combination to cause a complaint of insomnia in the general population. The common pathway to insomnia among these factors is heightened arousal (Buysse, 2003) (see Figure 2). An overlay of behavioral and conditioning factors may perpetuate the issue even after the initiating factor or cause resolves. Evidence is increasing that altered physiology directly related to the cancer process may play a prominent role in disrupting sleep, circadian rhythms, and hypothalamic-pituitary-adrenal (HPA) axis regulatory processes. Likewise, disrupted HPA axis and circadian rhythms may result in disturbed sleep and increased risk of cancer. Circadian rhythm models of activity, hormones, and cytokines have guided studies showing disrupted rhythms in patients with cancer with sleep-wake disturbances and symptom clusters that include fatigue, loss of appetite, depression, and pain (Abercrombie et al., 2004; Levin et al., 2005; Rich, 2007; Rich et al., 2005; Sephton & Spiegel, 2003). Evidence reveals that the risk of developing cancer is increased in shift workers. Circadian rhythm models have confirmed that many shift workers have circadian disruption, altered nighttime melatonin levels, and disrupted reproductive hormone profiles (Davis, Khoshknabi, & Yue, 2006).

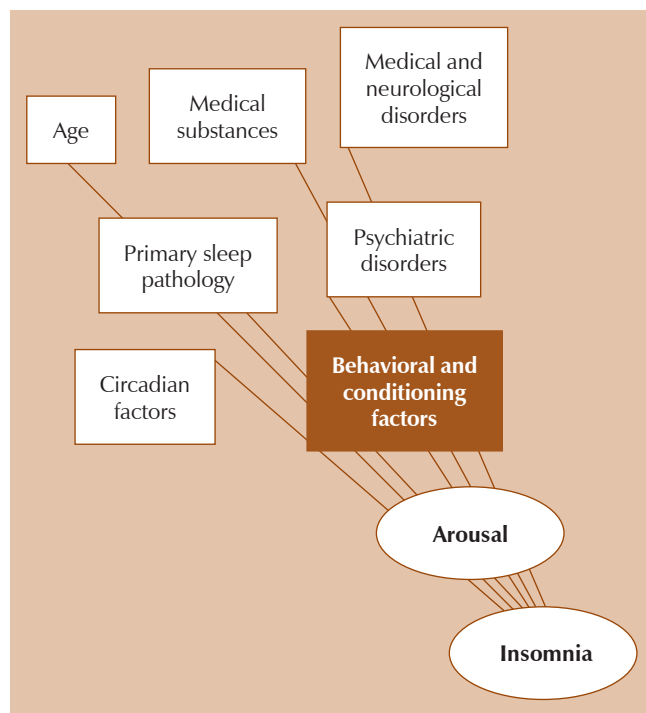
Familiarity with the theories, models, and frameworks related to sleep-wake disturbances in adult patients with cancer is essential (Otte & Carpenter, 2009). The Two-Process Model of Sleep Regulation serves as the foundation for testing the effectiveness of sleep interventions. The model is based on the interaction of two key processes, the homeostatic process S and the circadian process C (Achermann & Borbély, 2003; Berger, 2006). Vena, Parker, Cunningham, Clark, and McMillan (2004) adapted the model to include demographic, lifestyle, disease-related, treatment-related, and psychological factors. However, no report testing the factors in the revised model in patients with cancer was found. The Conceptual Model of Impaired Sleep (Lee, 2003) and the 3-P (predisposing, precipitating, and

perpetuating) Model (Spielman & Glovinsky, 2004) are additional models that are applicable for studying sleep in patients with cancer; however, only one study using the 3-P Model was found (Epstein & Dirksen, 2007). The 3-P Model depicts how the three factors can interfere with homeostatic process S and heighten arousal, which results in an individual exceeding the insomnia threshold (Perlis, Jungquist, Smith, & Posner, 2008).

Many studies testing interventions for sleep-wake disturbances in patients with cancer have been based on well-established theoretical models, often the Cognitive Behavior Model (Espie et al., 2008; Savard, Simard, Ivers, & Morin, 2005). Psychologically based models, including mindfulness models, also have been used (Carlson & Garland, 2005; Cohen, Warneke, Fouladi, Rodriguez, & Chaoul-Reich, 2004; Page, Berger, & Johnson, 2006). Most studies did not identify a theoretical basis for the investigation (Berger et al., 2005; Otte & Carpenter, 2009).

## Measurement

Berger et al. (2005) identified measurement as one of the major challenges facing sleep researchers studying patients with cancer and their caregivers. A review of descriptive studies prior to 2004 found that different



**Figure 2. Multiple Factors Acting Singly or in Combination to Cause a Complaint of Insomnia**

Note. From "Diagnosis and Classification of Insomnia Disorders" (p. 8), by D.J. Buysse in M.P. Szuba, J.D. Kloss, and D.F. Dinges (Eds.), *Insomnia: Principles and Management*, 2003, Cambridge, United Kingdom: Cambridge University Press. Copyright 2003 by Cambridge University Press. Reprinted with the permission of Cambridge University Press.

parameters were used to define *difficulty sleeping*. Nine parameters of sleep-wake disturbances were proposed to provide a common language for measurement of sleep-wake disturbances in patients with cancer and their caregivers (Berger et al., 2005). These parameters are similar to the eight sleep measures proposed for assessment of insomnia in the general population (Buysse, Ancoli-Israel, Edinger, Lichstein, & Morin, 2006). Many studies have relied on instruments that include a single item to describe difficulty sleeping (Berger, Sankaranarayanan, & Watanabe-Galloway, 2007). Because of the complex nature of the symptom, no single item or parameter is recommended to screen for sleep-wake disturbances in patients with cancer or in the general population (Sateia & Lang, 2008).

Current recommendations for measuring sleep-wake disturbances in patients with cancer are to consider using subjective and objective measures (Erickson & Berger, in press). Sleep quality is a perception, and measuring that perception is important. The Pittsburgh Sleep Quality Index (PSQI) remains the standard of self-reported research instruments, despite reports of its closer association with psychological and other symptom ratings than to objective sleep measures (Buysse et al., 2008; Regestein et al., 2004). A daily diary recording of a patient's perceptions of sleep-wake patterns for two weeks also yields this data (Morin & Espie, 2003).

Polysomnography (PSG) is the standard for detecting specific sleep and wake states (de Souza et al., 2003). PSG and actigraphy complement self-reported sleep perceptions, but the objective measures do not necessarily relate closely with self-reports (Buysse et al., 2008; Lauderdale, Knutson, Yan, Liu, & Rathouz, 2008). PSG provides in-depth information about stages of sleep, and in-home ambulatory PSG can be used to gather detailed data regarding the sleep-wake patterns of patients in their natural environments. PSG was effective in identifying severe difficulty with state maintenance or the ability to maintain the day waking and night sleep states in patients with advanced cancer (Parker et al., 2008). Wrist actigraphy is used to record movement over time in the form of activity counts, thereby providing an indirect measurement of sleep (Berger, Wielgus, et al., 2008). Estimates of sleep with actigraphy correlate at about 90% agreement with PSG (Cole, Kripke, Gruen, Mullaney, & Gillin, 1992) but are less likely to have self-reported sleep (Lauderdale et al.). A feature of wrist actigraphy is that data are collected in patients' natural environments.

The Insomnia Severity Index (Savard et al., 2005) has been validated for use as a screening tool to detect sleep disturbances in patients with cancer in research and clinical settings. The Clinical Sleep Assessment (CSA) for Adults and the CSA for Children have been validated for use as brief assessments for sleep disturbances in clinical settings (Lee & Ward, 2005). The CSA

instruments need additional clinical testing but have strengths of easy administration and scoring for research purposes and excellent face validity. Weaknesses include that their assessment is limited to insomnia, which is one of several sleep disorders that may be present in patients with cancer (American Academy of Sleep Medicine, 2005). The National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) roadmap initiative was designed to develop, validate, and standardize item banks to measure patient-reported outcomes in domains of self-reported health (Cella et al., 2007). Self-reported items for sleep disturbance and wake disturbance have been developed and are ready for testing in a variety of clinical populations (Garcia et al., 2007).

## Interventions

### Nonpharmacologic

Beginning in 2000, an increasing number of descriptive and intervention studies reported on sleep-wake disturbances in patients with cancer (Clark, Cunningham, McMillan, Vena, & Parker, 2004). A search of MEDLINE®, CINAHL®, and PsycINFO in March 2005 identified 20 intervention studies that examined sleep-wake disturbances in adult patients with cancer. Berger et al. (2002, 2003) were counted as one study. The studies were presented in the state of the science paper (Berger et al., 2005). A review and categorization of all intervention studies were repeated in December 2005 during preparation of the ONS Putting Evidence Into Practice (PEP) sleep-wake disturbances card. The categories were cognitive behavioral therapy and complementary, education or information, and exercise interventions (Page et al., 2006). An ONS PEP weight of evidence classification (see Figure 3) was assigned to each intervention category (Mitchell & Friese, n.d.).

A medical librarian assisted in a repeat search of MEDLINE, CINAHL, and PsycINFO in May 2008 to identify intervention studies from 1994–2008 that examined sleep-wake disturbances in adult patients with cancer (Page & Berger, 2009). Keywords used for the search were *sleep*, *sleep disturbance*, *intervention*, *insomnia*, and *cancer*. To be included, the intervention needed to be aimed at improving sleep and include sleep as a primary or secondary outcome. Members of the PEP sleep-wake disturbance team (Page & Berger) reviewed and synthesized the results. A similar search was repeated on January 6, 2009, during preparation of this article. Soden, Vincent, Craske, Lucus, and Ashley (2004) had been missed in the earlier review and is included here. A total of 18 new nonpharmacologic intervention studies have reported sleep-wake disturbance outcomes in adult patients with cancer since March 2005. Key data regarding the 18 new studies published since the March 2005 search are summarized

### Recommended for Practice

Interventions for which effectiveness has been demonstrated by strong evidence from rigorously conducted studies, meta-analyses, or systematic reviews, and for which expectation of harms is small compared with the benefits

### Likely to Be Effective

Interventions for which effectiveness has been demonstrated by supportive evidence from a single rigorously conducted controlled trial, consistent supportive evidence from well-designed controlled trials using small samples, or guidelines developed from evidence and supported by expert opinion

### Benefits Balanced With Harms

Interventions for which clinicians and patients should weigh the beneficial and harmful effects according to individual circumstances and priorities

### Effectiveness Not Established

Interventions for which there are currently insufficient or conflicting data or data of inadequate quality, with no clear indication of harm

### Effectiveness Unlikely

Interventions for which lack of effectiveness has been demonstrated by negative evidence from a single rigorously conducted controlled trial, consistent negative evidence from well-designed controlled trials using small samples, or guidelines developed from evidence and supported by expert opinion

### Not Recommended for Practice

Interventions for which lack of effectiveness or harmfulness has been demonstrated by strong evidence from rigorously conducted studies, meta-analyses, or systematic reviews, or interventions where the costs, burden, or harms associated with the intervention exceed anticipated benefit

### Expert Opinion

Low-risk interventions that are (1) consistent with sound clinical practice, (2) suggested by an expert in a peer-reviewed publication (journal or book chapter), and (3) for which limited evidence exists. An expert is an individual with peer-reviewed journal publications in the domain of interest.

### Figure 3. Weight of Evidence Classification

Note. From "ONS Putting Evidence Into Practice Weight of Evidence Classification Schema: Decision Rules for Summative Evaluation of a Body of Evidence," by S. Mitchell and C.R. Friese, n.d. Retrieved January 14, 2009, from <http://www.ons.org/outcomes/tables/documents/woevidence.pdf>. Copyright 2009 by Oncology Nursing Society. Adapted with permission.

in Table 1. Any study that combined two intervention categories was counted only once and assigned to the category where reviewers decided it fit best. The total number of intervention studies is 38.

Most of the newer studies supported the findings and original PEP classification for that category of intervention. The major revision to the 2009 PEP sleep-wake disturbance card was that cognitive behavioral therapy was moved to the "likely to be effective" classification. This recommendation was based on results of four large positive intervention studies (Arving et al., 2007; Berger, Kuhn, et al., 2008; Epstein & Dirksen, 2007; Espie et al., 2008). Several studies reported positive benefits of complementary therapies on sleep-wake disturbances,

but only one was a large, randomized controlled trial (RCT) (Cohen & Fried, 2007). Of the two education or information studies (Palesh et al., 2007; Williams & Schreier, 2005), neither had positive outcomes. The two exercise intervention studies (Payne, Held, Thorpe, & Shaw, 2008; Rabin, Pinto, Dunsiger, Nash, & Trask, 2008) reported positive benefits on sleep, and one combined relaxation with exercise to promote sleep. More large RCTs are needed before concluding that cognitive behavioral therapy is effective and is "recommended for practice" and to demonstrate that complementary therapies, education or information, and exercise interventions are "likely to be effective" in reducing sleep-wake disturbances in adult patients with cancer.

**Cognitive behavioral therapy:** This intervention is designed to eliminate the perpetuating factors responsible for chronic insomnia. The goal of acute treatment is to reduce perpetuating factors below the insomnia threshold and to decondition the hyperarousal response (Perlis et al., 2008). A positive response to treatment occurs when perpetuating factors are reduced below the threshold. Cognitive behavioral therapies assist with sleep initiation and maintenance. The 2006 AASM practice parameters (Morganthaler et al., 2006) recommended psychological and behavioral interventions as effective and recommended them as the standard for treating chronic comorbid insomnia. AASM also recommended, as standard, three specific therapies for chronic insomnia: stimulus control, relaxation, and cognitive behavioral therapy. Sleep restriction and multicomponent therapy were among the therapies rated by AASM as a guideline for treating chronic insomnia. Examination of evidence to date reveals that four RCTs (Arving et al., 2007; Berger, Kuhn, et al., 2008; Epstein & Dirksen, 2007; Espie et al., 2008) and nine quasi-experimental studies (Berger et al., 2002, 2003; Carpenter, Neal, Payne, Kimmick, & Storniolo, 2007; Cohen & Fried, 2007; Davidson, Waisberg, Brundage, & MacLean, 2001; Hunter, Coventry, Hamed, Fertiman, & Grunfeld, 2008; Quesnel, Savard, Simard, Ivers, & Morin, 2003; Savard et al., 2005, 2006) have tested cognitive behavioral therapy techniques in patients with a variety of cancer diagnoses at various times along the continuum of care. Most studies reported improvement in several sleep outcomes using a variety of measures, most commonly perceived sleep quality using PSQI. Among the RCTs, two were conducted in the active phase of treatment (Arving et al.; Berger, Kuhn, et al.) and two were conducted with survivors (Epstein & Dirksen; Espie et al., 2008). Additional evidence from several smaller studies in the survival phase supported these positive findings. The cognitive behavioral interventions varied in content, length, frequency, and delivery and measured sleep-wake outcomes in patients with cancer with varied diagnoses. Despite these limitations, evidence is increasing that this intervention improves sleep in patients with cancer.

**Table 1. Nonpharmacologic Intervention Studies for Sleep-Wake Disturbances in Patients With Cancer<sup>a</sup>**

Study	Design	Tool	Sleep Outcome	Limitations
<b>Cognitive Behavioral Therapy—PEP Weight of Evidence Category: Likely to Be Effective</b>				
Arving et al., 2007	RCT	EORTC-QLQ-BR23	Positive <sup>b</sup>	Minor
Berger et al., 2008	RCT	PSQI Sleep diary Actigraphy	Positive Positive <sup>c</sup> Negative	Minor
Carpenter et al., 2007	Pre-/ post-test	PSQI Actigraphy	Negative Negative	Minor
Epstein & Dirksen, 2007	RCT	Sleep diary Actigraphy	Positive <sup>b</sup> Positive <sup>d</sup>	Minor
Espie et al., 2008	RCT	PSQI Epworth Sleepiness Scale Sleep diary Actigraphy	Positive <sup>e</sup> Not reported Negative Negative	Minor
Hunter et al., 2008	Pre-/ post-test	WHQ	Positive	Minor
Savard et al., 2005	Two-group WLC	Insomnia Interview Schedule Structured Clinical Interview for the DSM-IV Sleep diary PSG ISI	Positive Positive <sup>f</sup> Negative Positive	Minor
Savard et al., 2006	Two-group WLC	ISI Structured Clinical Interview for the DSM-IV EORTC-QLQ-BR23	Negative Not reported Negative	Minor
<b>Complementary Therapies—PEP Weight of Evidence Category: Effectiveness Not Established</b>				
Carlson & Garland, 2005	One group	PSQI	Positive	Major
Cohen & Fried, 2007	RCT	MSQ	Positive	Minor
de Moor et al., 2008	RCT	PSQI	Negative	Minor
Elkins et al., 2008	RCT	MOS-Sleep	Positive	Minor
Soden et al., 2004	RCT	Verran and Snyder-Halpern Sleep Scale	Positive	Major
van den Berg et al., 2006	Pre-/ post-test	EORTC-C30	Negative	Major
<b>Education or Information Intervention—PEP Weight of Evidence Category: Effectiveness Not Established</b>				
Palesh et al., 2007	RCT	Sleep questionnaire	Negative	Minor
Williams & Schreier, 2005	RCT	Modified self-care diary	Negative	Major
<b>Exercise—PEP Weight of Evidence Category: Effectiveness Not Established</b>				
Payne et al., 2008	Pilot	PSQI Actigraphy	Positive <sup>d</sup> Positive	Minor
Rabin et al., 2008	Pilot	PSQI	Positive	Minor

<sup>a</sup> Studies were released after publication of Berger et al., 2005; <sup>b</sup> SOL, WASO, total sleep time, time in bed, sleep efficiency, and sleep quality; <sup>c</sup> WASO minutes and sleep efficiency; <sup>d</sup> SOL, WASO, total sleep time, and time in bed; <sup>e</sup> SOL, WASO, total sleep time, and sleep efficiency; <sup>f</sup> SOL, WASO, sleep efficiency, and total wake time

DSM-IV—Diagnostic and Statistical Manual (4th ed.); EORTC-C-30—European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EORTC-QLQ-BR23—European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire With Breast Cancer; ISI—Insomnia Severity Index; MOS-Sleep—Medical Outcomes Study Sleep Scale; MSQ—Mini Sleep Questionnaire; PEP—Putting Evidence Into Practice; PSG—polysomnography; PSQI—Pittsburgh Sleep Quality Index; RCT—randomized controlled trial; SOL—sleep onset latency; WASO—wake after sleep onset; WHQ—Women's Health Questionnaire; WLC—wait-list control

Note. Positive sleep outcome findings were significant at  $p < 0.05$ .

**Complementary therapies:** Six RCTs and 11 quasi-experimental studies that described use of a variety of complementary therapies in adult patients with cancer were found. Studies were organized according to type of complementary intervention. Sleep quality was improved in one RCT and four quasi-experimental trials that tested Mindfulness-Based Stress Reduction (MBSR), a combination of relaxation techniques, meditative techniques, and yoga therapy in patients with breast cancer, early prostate cancer, and a mixed group of other cancer populations (Carlson & Garland, 2005; Carlson, Spica, Patel, & Goodey, 2003, 2004; Cohen et al., 2004; Shapiro, Bootzin, Figueredo, Lopez, & Schwartz, 2003). A large RCT tested cognitive therapy versus relaxation and guided imagery with a control condition in patients with breast cancer receiving chemotherapy or radiation therapy 2–12 months after surgery. The interventions reduced psychological distress in both groups compared to controls. However, the relaxation and guided imagery intervention was more effective in reducing levels of fatigue and sleep difficulties (Cohen & Fried, 2007).

Two quasi-experimental studies using mixed cancer populations found that autogenic training had favorable sleep outcomes (Simeit, Deck, & Conta-Marx, 2004; Wright, Courtney, & Crowther, 2002). Supportive-expressive group therapy interventions resulted in decreased wake-after-sleep-onset time in a quasi-experimental study of patients with breast cancer (Fobair et al., 2002). One RCT with newly diagnosed stage IV patients with metastatic renal cell cancer showed improvement in four measured areas of sleep disturbance when using expressive writing (de Moor et al., 2002). Another randomized study using expressive writing in women who received neoadjuvant breast cancer chemotherapy found no benefit to sleep disturbances in the period between three days prior and two weeks after surgery (de Moor et al., 2008).

Progressive muscle relaxation was tested in an RCT with patients who had a variety of cancer diagnoses and showed reduced sleep latency (Cannici, Malcolm, & Peek, 1983). One RCT reported that a hypnosis intervention used to treat hot flashes in breast cancer survivors significantly decreased hot flashes and improved sleep compared to the control condition (no treatment) (Elkins et al., 2008). Healing touch showed improvement on self-reported sleep disturbances in a quasi-experimental study using a sample with various cancer diagnoses (Weze, Leathard, Grange, Tiplady, & Stevens, 2004). Two studies looked at the use of massage and showed mixed results (Smith, Kemp, Hemphill, & Vojir, 2002; Soden et al., 2004). A haptotherapy intervention (van den Berg, Visser, Schoolmeesters, Edelman, & van den Borne, 2006), which uses touch therapy to assist patients to connect with their feelings and learn how to deal with their illness, did not improve QOL or sleep quality in the intervention group compared to the control group.

Studies in this category vary widely in content, frequency, and delivery of the complementary intervention and the outcomes measured in patients with cancer with varied diagnoses. Evidence is increasing that complementary interventions, particularly MBSR, improve sleep in patients with cancer, but results from RCT studies are needed.

**Education or information:** Three studies have tested the benefits of an education or information intervention on sleep-wake disturbances. Favorable sleep outcomes were found in an RCT using an informational tape as an educational intervention with men receiving radiation for localized prostate cancer (Kim, Roscoe, & Morrow, 2002). No changes in sleep disturbances were found in an RCT using informational audiotapes with women with breast cancer undergoing chemotherapy (Williams & Schreier, 2005) or in an RCT using supportive-expressive group therapy (Palesh et al., 2007). More evidence is needed to evaluate the effects of education or information interventions in improving sleep in patients with cancer.

**Exercise:** Only five quasi-experimental or small RCT studies have shown favorable sleep outcomes when using aerobic exercise interventions. Three were tested in patients with breast cancer (Mock et al., 1997; Payne et al., 2008; Rabin et al., 2008) and one with patients with a variety of cancers (Young-McCaughan et al., 2003). A small pilot RCT examining the effects of exercise on sleep in multiple myeloma patients was inconclusive because of a high attrition rate (42%) (Coleman et al., 2003). Existing evidence shows a positive trend for exercise interventions to improve sleep in patients with cancer, but results from larger studies are needed.

## Pharmacologic

No intervention studies have tested the effects of prescription sleep drugs in patients with cancer. An intervention trial tested the efficacy of low and high doses of the antidepressant venlafaxine hydrochloride for hot flashes and associated sleep disturbances after breast cancer and reported mixed but generally no effects on sleep (Carpenter, Storniolo, et al., 2007). Concerns have been raised of potential drug-drug interactions that may reduce the effectiveness of tamoxifen when taken with selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors (Sateia & Lang, 2008).

## Implications for Practice, Health Policy, Education, and Research

### Practice

The ability to translate knowledge from research to practice to reduce the negative health outcomes of sleep-wake disturbances in adult patients with cancer

has risen dramatically since the 2004 conference. Screening tools to detect sleep-wake disturbances, such as the CSA (adult), the Insomnia Severity Index (ISI), and the PROMIS sleep and wake disturbance items, are ready for testing in oncology clinical practice. Nurses can deliver evidence-based interventions for insomnia, as has been shown to be effective in controlled research studies (Espie et al., 2007, 2008). Clinicians are instructed to identify interventions with the highest level of evidence on the PEP cards and integrate them into the plan of care based on patient status, acceptability, and expectations (ONS, 2005). Background for the current atmosphere will now be presented to increase understanding of current opportunities.

A white paper on nursing-sensitive patient outcomes (NSPOs) (Given & Sherwood, 2005) illustrated how a focus on NSPOs in research and policy development could stimulate oncology nurses to drive future quality oncology clinical care. Oncology researchers have a responsibility to evaluate NSPOs, such as sleep quality, and to frame clinical research studies in the context of clinical outcomes (Berger & Mitchell, 2009). Two major clinical challenges are gathering resources to implement wide adoption of clinical sleep tools to consistently measure NSPOs before and after intervention and standardizing key patient and organizational indicators of NSPOs for databases.

A high priority is for researchers to test the efficacy and effectiveness of measurements and interventions in clinical care. Large, multisite implementation studies are needed that use diverse samples, multiple outcomes (including cost), and comparison conditions, such as current standard of care or alternative programs. These studies will be critical to determining whether the effectiveness of the sleep-wake disturbance PEP card interventions on NSPOs varies by disease, stage, or ethnic, racial, or cultural characteristics. Dissemination of research studies also will provide empirical validation of intervention adaptation procedures (Solomon, Card, & Malow, 2006) and will provide evidence to support widespread application and generalizability of research findings (Glasgow & Emmons, 2007; Green & Glasgow, 2006; Sussman, 2006).

A second high priority is for oncology practice settings to create the infrastructure to initiate and sustain evidence-based practice (Berger & Mitchell, 2009). Clinical leaders should understand characteristics of practice change to overcome clinical care inertia. Leaders are called upon to develop a practice culture that promotes daily application and enthusiastic adoption of evidence-based practice in nursing care delivery (Glasgow, Lichtenstein, & Marcus, 2003; Stetler, Ritchie, Rycroft-Malone, Schultz, & Charns, 2007). A culture that lists evidence-based functions for each committee and council and uses expectations for evidence-based practice in all performance appraisals has greater

likelihood of success than one that only speaks to its importance. Sustaining an evidence-based culture requires opportunities for staff orientation and education to learn essential knowledge and skills about evidence-based practice (Milner, Estabrooks, & Humphrey, 2005; Milner, Estabrooks, & Myrick, 2006). ONS and other providers can assist by developing short courses and conferences to promote an evidence-based practice culture in a variety of settings. Improving researchers' understanding of the business side of research translation is beneficial and can lead to inclusion of a translation plan for each research project. Clearly, many challenges and opportunities exist to promote adoption of evidence-based practice in regard to sleep-wake disturbances.

## Health Policy

A powerful strategy to promote the adoption of research innovations in clinical practice lies in the development of health policy. An example of efforts to translate cancer research into practice through policy development has been in the area of tobacco control (Malone, 2006; Sarna & Bialous, 2006). Other examples of promoting uptake of innovations include the creation of a position paper (Mooney, 2004) and analysis of results within a health policy framework (Poirier, 2005, 2006).

The National Sleep Foundation (2008) has supported efforts to teach Americans the benefits of adequate sleep and the dangers of driving when drowsy. One large county school district in Kentucky established a policy to start school one hour later for adolescents and saw a meaningful increase in hours of adolescent sleep and a 16.5% decrease in the number of automobile crashes by teen drivers in the county over two years (Danner & Phillips, 2008). The U.S. Food and Drug Administration (2007) revised the labeling text for zolpidem tartrate extended-release tablets to reflect an increased likelihood of sleep-driving and other complex behaviors. This is another example of health policy promoting the health and welfare of the general public. Another strategy to promote diagnosis and treatment of sleep-wake disorders has been development of a health policy to include evaluation in a sleep center as a covered medical expense on health insurance policies.

A high priority is for health policy development to occur in conjunction with payers and regulatory agencies (American Society of Clinical Oncology, 2006; Gajewski et al., 2005). Reimbursement substantially influences care delivery. Researchers, clinicians, and payers must work together so that reimbursement policies for sleep-wake disturbances are informed by research evidence and those researchers address questions important in developing reimbursement policies.



## Education

Berger et al. (2005) listed specific implications for nursing education related to sleep-wake disturbances. A high priority is for nursing education to include information on sleep and circadian rhythms (Lee et al., 2004). Only one publication was found that described implementation of these recommendations by an academic institution. An online, four-credit, geriatric-focused course in a nurse practitioner curriculum was developed to address the challenge of meeting the healthcare needs, including sleep, of older adults (Scherer, Bruce, Montgomery, & Ball, 2008).

Another publication outlined a statewide effort in newborn nurseries to promote a “back to sleep” clinical nursing curriculum and training program. Short-term positive effects were noted on risk-reduction adherence in the setting where parents first observe safe sleep behavior (Price, Hillman, Gardner, Schenk, & Warren, 2008).

## Research

Many implications for research to improve sleep and daytime sleepiness or wakefulness in adult patients with cancer were identified in Berger et al. (2005). Areas of progress include exploration of the etiology of symptom clusters and relationships among several symptoms with insomnia and the development, testing, and dissemination of interventions in which sleep was the primary outcome. Researchers should secure funding to initiate and sustain programs of research in the identified areas.

Future research reports should describe the delivery, receipt, and enactment of the intervention (Resnick et al., 2005). Priorities for future multidisciplinary research are listed in Figure 4. Researchers should address methodologic challenges and limitations identified by investigators in the design and analysis of sleep intervention studies, particularly when the sample is older, is symptomatic from cancer or comorbid conditions, or has recurrent cancer (Visovsky, Berger, Kosloski, & Kercher, 2008). Intervention fidelity is critical to appraisal of an intervention’s effectiveness.

## Summary

Considerable progress has been made since 2004 in raising awareness of the prevalence and identifying effective interventions to improve sleep-wake disturbances in adult patients with cancer. Particular strengths of recent work include several RCT studies using cognitive behavioral therapy interventions that reported improved sleep quality in adult patients with cancer, fairly consistent use of multi-item measures with established reliability and validity, and studies focusing on breast cancer survivors with chronic insomnia.

- Determine the frequency, severity, and distress of sleep-wake disturbances in patients with cancer with various diagnoses, in different stages of disease, and with varied treatment regimens.
- Determine the effects of difficulty falling asleep, maintaining sleep, early morning awakening, and nonrestorative sleep on sleep quality, immune function, hypothalamic-pituitary-adrenal axis function, circadian function, disease-free period, quality of life, and overall survival.
- Identify isolated and common mechanisms that lead to sleep-wake disturbances.
- Use conceptual models to study sleep-wake disturbances. Identify advantages and limitations of models used to test the effectiveness of interventions to promote sleep initiation, maintenance, and daytime functioning.
- Test methods to adopt screening for sleep-wake disturbances in the clinical setting.
- Use well-established multi-item subjective measurements.
- Incorporate objective sleep measures (polysomnography, actigraphy) and biomarkers related to sleep (melatonin, cortisol, C-reactive protein, core body temperature, immune markers, genetic markers, ghrelin, leptin, orexin, and glucose tolerance).
- Test the frequency, duration, and dose of a behavioral intervention.
- Establish the efficacy of behavioral interventions in a variety of clinical care settings and populations.
- Conduct dissemination research studies to provide empirical validation of intervention adoption procedures.

### Figure 4. Recommendations for Multidisciplinary Research on Sleep-Wake Disturbances in Adult Patients With Cancer

Limitations include the many studies in which sleep has been a secondary outcome, measured by a single item, without an identified conceptual basis for the intervention, and variations in content, length, frequency, and delivery of interventions. In addition, samples have primarily been patients with breast cancer, with fewer studies including patients with other cancer diagnoses and at different times along the illness trajectory. Cognitive behavioral therapy interventions are likely to be effective, and complementary, education or information, and exercise interventions offer promise but need additional testing in RCT studies.

Ann M. Berger, PhD, RN, AOCN®, FAAN, is a professor and the Dorothy Hodges Olson Endowed Chair in Nursing, the director of the doctoral program, and an advanced practice nurse in the College of Nursing at the University of Nebraska Medical Center in Omaha. Funding for this study was provided by the National Institutes of Health and the National Institute of Nursing Research (5R01 NR00762-05). This article was presented at the State of the Science Lecture at the Cancer Nursing Research Conference in Orlando, FL, in February 2009. Berger can be reached at [aberger@unmc.edu](mailto:aberger@unmc.edu), with copy to editor at [ONF\\_Editor@ons.org](mailto:ONF_Editor@ons.org). (Submitted January 2009. Accepted for publication March 7, 2009.)

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